REMARKS

Claims 39-50 are presently pending in the subject application. Claim 40 is cancelled without prejudice or disclaimer. Claims 39, 41, 42, 44, 46, 47, and 49 are amended in the instant response to more particularly point out and distinctly claim the subject matter, which Applicants regard as their invention. Therefore, the claims now under consideration are claims 39 and 41-50 as amended. These amended claims are supported by the specification as filed, and Applicants believe that no new matter has been added. For example, support for the amendment to claim 39 is found in Examples 2 and 3 and Figures 3 and 4 and, specifically, on page 13, line 10. Applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection of the claims.

Withdrawal of claim 47

Claim 47 has been withdrawn by the Examiner as being drawn to a non-elected invention. Applicants respectfully traverse.

As set forth in M.P.E.P. § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions: 1) the inventions must be independent or distinct as claimed, and 2) there must be a serious burden on the examiner if restriction is required.

With respect to the second criteria, Applicants respectfully submit that the Examiner has made no showing that there would be a serious burden to examine claim 47. Claim 47 recites specific additional compounds, and is dependent on claim 46, which recites "at least one additional compound" generally. Therefore, as claim 47 is dependent on claim 46 and in view of the examination of claim 46, examination of claim 47 does not present a serious burden on the Examiner.

Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 39-46 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. More specifically, according to the Examiner, the present specification reveals no specific test data to support the generic limitations. Applicants respectfully traverse.

The M.P.E.P. states that: "A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled" M.P.E.P. § 2164.02, paragraph 5. Further, "[a]n applicant need not have actually reduced the invention to practice prior to filing." M.P.E.P. 2164.02, citing *Gould v Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). Also, the C.C.P.A. has stated that the specification need not contain a working example of every embodiment of the invention "if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it." *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). *See, United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988).

The present claims are directed to a method of increasing brain cytidine levels. Example 2 and associated Figs 3 and 4 provide an animal model suitable for studies of human pyrimidine metabolism, with test results. Exemplary details are provided for a suitable administration regime with the recitation, among others, that "[g]erbils are given uridine orally" (see page 12, line 13). Moreover, Example 2 teaches the analysis of cytidine levels in the cerebrospinal fluid of human patients, reciting that "in humans . . . the CSF levels are measured" (see page 12, line 21 to page 13, line 1). In addition, Example 3 provides specific dosage regimes for both male and female patients. Thus, working examples are provided contrary to the Examiner's assertions.

Further, specific support is found for "neurological disorders" in the specification as filed, including Example 6 directed to ataxias, Example 7 directed to tardive dyskinesia, Example 8 directed to strokes, Example 9 directed brain trauma, Example 10 directed to neuromuscular disorders, and Example 11 directed to schizophrenia and Parkinson's disease.

Support for "memory disorders" is also found in the specification as filed, including Example 3, directed to memory disorders and cognitive dysfunctions, including both pathological and non-pathological dementias. Support for "memory disorder associated with aging" is found in the specification as filed, including Example 3 directed to non-pathological dementia associated with aging.

For at least these reasons, Applicants respectfully request the withdrawal and reconsideration of this rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 39-46 and 48-50 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More specifically, the Examiner asserted that claim 39 is an incomplete method-of-treating claim because it fails to include a specific disease condition to be treated. Applicants respectfully traverse.

Claim 39 is directed to a method of increasing brain cytidine levels. While long desired, increasing brain cytidine level has been problematic due to the blood brain barrier. The present applicants discovered that the administration of either uridine or a precursor of uridine leads to increased systemic and brain cytidine. Thus, Claim 39 recites "[a] method of increasing brain cytidine levels in a human in need thereof" by administering uridine or a precursor thereof. Claim 39 is not indefinite, as one of ordinary skill in the art would clearly understand the metes and bounds of the presently claimed invention. Reconsideration is respectfully requested

The Examiner further found that claims 41, 42 and 45 lacked proper antecedent basis and/or failed to further limit any patentable feature of independent claim 39. Claims 41 and 42 have been amended to overcome this rejection. Claim 41 as amended herein is dependent upon claim 39 and includes the further limitation: "wherein increasing said brain cytidine levels inhibits or ameliorates a neurological disorder." Claim 42 as amended herein is dependent upon

claim 39 and includes the further limitation: "wherein increasing said brain cytidine levels inhibits or ameliorates a memory disorder." Reconsideration is respectfully requested.

The Examiner also found that claims 39, 40, 43, 44 and 50 were indefinite for reciting "uridine or a precursor thereof" which is a "functional term directed to chemical species" which "lacks adequately defined metes and bounds." Applicants respectfully traverse.

The M.P.E.P. requires that claims be allowed "which define the patentable subject matter with a *reasonable* degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted" M.P.E.P. 2173.02, paragraph 1. (Emphasis in the original).

Applicants maintain that the term "a precursor thereof" would be understood to one of skill in the art. One of skill in the art would clearly understand that a precursor of uridine is a compound that can be converted to uridine when subjected to metabolic processes. Thus, the term uridine precursor is not indefinite as one of ordinary skill in the art would clearly understand the metes and bounds of the term. Further, precursor is defined in the specification as follows:

> The terms 'uridine precursor' or uridine source' or uridine prodrug' are used interchangeably and as defined hereinafter mean compounds, e.g., uridine salts or food products containing uridine, that transform into uridine upon administration to a host such as human.

Page 7, Lines 1-4.

Reconsideration is respectfully requested.

The Examiner also found that the term "a neurological disorder" in claim 41 and the term "memory disorder" in claims 42 and 45 rendered these claims indefinite. Applicant respectfully traverses. The Federal Circuit has held that claims will not be held invalid for indefiniteness so long as "those skilled in the art" would understand the scope of the claim when the claim is read in light of the specification." *North American Vaccine, Inc. v. American Cyanamid Cop.*, 7 F.3d 1571, 1579 (Fed. Cir. 1993). As discussed above, these terms are clearly defined in the present specification and are therefore not indefinite. Reconsideration is respectfully requested.

The Examiner further rejected claim 46 because the term "a second compound" is allegedly indefinite. Applicants respectfully traverse.

One of ordinary skill in the art would clearly understand the metes and bounds of this claim. The claim encompasses the administering (1) an effective amount of uridine or a precursor thereof; and (2) administering an effective amount of at least one additional compound. Clearly, as acknowledged by the Examiner, this claim limitation is not intended to include "obviously inappropriate embodiments," which one of ordinary skill in the art would never consider. Accordingly, the scope of this term is not indefinite, as one of ordinary skill in the art would understand the meaning of the term with "a reasonable degree of particularity and distinctness." Reconsideration is respectfully requested.

The Examiner found that claim 48 was indefinite because the term "or mixtures thereof" inappropriately expands the scope of claim 46 on which it depends. The Examiner rejected claim 49 for similar reasons. Applicants respectfully traverse.

Clearly, according to the present invention, the term "a compound" in claim 46 may be composed of a single component or a mixture of components. Therefore, the "compound" of claim 46 may be choline chloride or the "compound" may be choline chloride mixed with choline bitartrate, for example. Therefore, claims 48 and 49 are not indefinite as one of ordinary skill in the art would clearly understand the metes and bounds of the invention with "a reasonable degree of particularity and distinctness." In addition, Claim 46 has been further defined to read: "at least one additional compound". Reconsideration is respectfully requested.

Lastly, the Examiner rejected claim 49 as being indefinite for reciting "a uridine phosphorylase inhibitor," "a uridine secretion inhibiting compound," and "a uridine renal transport competitor." Applicants respectfully traverse.

These terms are generally well understood to one of ordinary skill in the art and therefore do not render the claim indefinite. Indeed, functional limitations are often used when claiming an innovation in the chemical arts. Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 39-46 and 48-50 under 35 U.S.C. § 102(b) or (e) over references cited as B, L, R, S, T, U, V, W, X, Y, and Z.

As amended, claim 39 recites a method of increasing brain cytidine levels in a human by administering an effective amount of uridine or a precursor thereof, wherein the dose of uridine is less than 300 mg/day.

Reference B (Piezza) is directed to the use of uridine as a growth promoter and recites that "uridine is capable not only or reverting [sic, of reversing] the harmful effects induced in cell cultures . . . but, and this is by far more important, that it can act as a growth promoter" (see column 3, line 31). Reference B relates to a cell growth promoter and further recites "we discovered that uridine can give the same results of the [sic, as] NGF when the growth factor is withdrawn from the medium" (see column 3, line 39). In contrast thereto, the invention teaches that "uridine administration in humans leads to increases in systemic and brain cytidine" (see page 6, lines 15-16). In other words, reference B discloses the use of uridine as a means of promoting cell growth, but does not disclose a method of increasing cytidine levels. In fact, reference B is completely silent on increasing cytidine levels and on the effect of uridine administration on cytidine levels.

Moreover, reference B discloses doses of 300-2000 mg/day in humans (see column 7, lines 54-55 and column 10, line 5). As amended, claim 39, specifies a dose of less than 300 mg/day. Therefore, claims 39-46 and 48-50 are not anticipated by reference B, as reference B does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day.

Reconsideration is respectfully requested.

Reference L (Polifarma) discloses the use of uridine to treat a decay in neuron functional activity in brain pathologies such as cerebral senility, cerebral hypoglycemia, cerebral hypoxemia or cerebral ischemia, with dosages of 1-5 g/day (see page 8, lines 20-21) or of 15 mg/kg (see page 5, line 6), which, even for a moderately small person of 50 kg corresponds to 750 mg. These doses are much higher than the doses contemplated by the instant invention.

Therefore, reference L does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference R (Page et al.) discloses treatment of diseases noted in the first few years of life with high doses of uridine of 1,000 mg/kg per day (see page 11603, paragraph 9). A dose of 1,000 mg/kg corresponds to 50,000 mg for a 50 kg person, which greatly exceeds the dosages claimed in the present invention. Moreover, reference R discloses that the dose was further increased to 150 mg/kg per day (see page 11604, paragraph 4). A dose of 150 mg/kg corresponds to 7,500 mg for a 50 kg person, which again, greatly exceeds the dosages claimed in the present invention. Therefore, reference R does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. In fact, reference R teaches away from the low doses claimed in the present invention. Reconsideration is respectfully requested.

Reference S (Coirault et al.) recites the use of uridine triphosphate to treat muscular atrophy of multiple origins or muscular fatigue. Reference S is silent on increasing brain cytidine levels. Therefore, reference S does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference T (Merlini et al.) the reference discloses the effects of large doses of cytidine and uridine) to hospitalized patients with mental deterioration. Reference T specifically requires "large doses" of cytidine and uridine together. Therefore, reference T does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference U (Gallai et al. I) discloses the use of uridine at doses of 300 mg/day for the treatment of patients with diabetic retinopahty. Therefore, reference U does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference V (Gallai et al. II) discloses the administration of uridine and cytidine to patients with multi-infarct dementia. Therefore, reference V does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference W (Drago et al.) discloses the effect of the administration uridine and cytidine on learning and memory. Reference W further teaches that the administration of either uridine or cytidine alone had no effect. In fact, reference W teaches away from the presently claimed invention. Therefore, reference W does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference X (Manna et al.) discloses the administration of uridine, cytidine and levoglutamamte to patients with chronic cerebrovascular diseases. Reference X also teaches that the use of any of these alone had no effect, which teaches away from the presently claimed invention. Therefore, reference W does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference Y (Keilbaugh et al.) discloses the use of uridine to treat a toxic peripheral neuropathy caused by giving the drug ddC to AIDS patients. Therefore, reference Y does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Reference Z (Popov et al.) discloses the administration of uridine to increase brain levels of UDP-glucose and uracil nucleotides. Therefore, reference Z does not teach or suggest a method of increasing brain cytidine levels by the administration of less than 300 mg of uridine a day. Reconsideration is respectfully requested.

Applicant's have surprisingly discovered that the administration of uridine increases brain cytidine levels. Prior to Applicant's invention, it was believed that uridine would compete with cytidine for transport from the blood to the brain. Such that, prior to the present invention, one would have thought that the administration of uridine would decrease brain cytidine levels,

rather than increase it, and thus exacerbate the memory/cognitive impairment sought to be treated. None of the references cited by the Examiner teach or suggest that administering uridine increases cytidine levels in the brain. Accordingly, for at least the foregoing reasons, the rejection under 35 U.S.C. § 102 of claims 39-46 and 48-50 over the cited references should be withdrawn.

CONCLUSION

In view of the forgoing remarks, it is respectfully submitted that claims 39-50 are in condition for allowance. An early action to that effect is cordially solicited.

If the Examiner believes there is any issue which could be resolved by a telephone or personal interview, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this Response, or credit any overpayment to Deposit Account No. 50-0436. In the event that an extension of time is required, or may be required in addition to that requested in a petition for an extension of time, the Commissioner is hereby requested to grant a petition for that extension of time which is required to make this response timely and is hereby

authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-1710.

Respectfully submitted,

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Date: August 1, 2002

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATIONS:

Please amend the specification as follows:

On page 6, the second full paragraph is amended as follows:

This invention is based upon the unexpected discovery that uridine administration in humans leads to increases in systemic and brain cytidine. While certain methods of treatment of certain neurological diseases using uridine are known, the prior art has heretofore failed to provide the methods of treatment of diseases which are objects of this invention. These and other objects of the invention will become more readily apparent from the following description.

On page 12, the first full paragraph is amended as follows:

Gerbils, rather than rats or other rodents, are selected for this example, as the pyrimidine metabolism of said gerbils is closer to humans. For practical and ethical reasons humans cannot always be used for certain experimental studies and those skilled in the art generally recognize that the gerbil model is equivalent to a human model. Indeed, gerbils are the [choice] model of choice for certain human diseases and brain disorders such as cerebral ischemia (Ginsburg et al., Rodent models of cerebral ischemia. *Stroke* 20:1627-1642, 1989). Gerbils are given [orally] uridine orally and 60 minutes later plasma and brain levels of cytidine and uridine are measured by the modified HPLC method described in Example 1. [The]Fig. 3 shows the relative ratio between uridine and cytidine levels in plasma after oral administration of 250 milligram per kg of body weight (mg/kg) of uridine. [The]Fig. 4 shows the relative ratio between uridine and cytidine levels in the brain after oral administration of 250 mg/kg of uridine. These results indicate that the metabolic processing of uridine in the brain is different than systemic processing of uridine in plasma. The results also indicate that uridine, when transported into the brain, is readily converted to cytidine and this conversion is more efficient in the brain than in plasma. Similar experiments are also carried out in humans wherein instead of measuring brain levels of nucleosides, the CSF levels are

measured. The finding that uridine is readily converted to cytidine especially in the brain is totally unexpected and constitutes the basis for the present invention.

IN THE CLAIMS:

Please amend the claims as follows:

39. (Amended) A method of increasing brain cytidine levels in a human in need thereof [of increased brain cytidine levels] comprising administering an effective amount of uridine or a precursor thereof, wherein the effective amount of uridine is less than 300 mg/day, and wherein the effective amount of the precursor is an amount that converts to less than 300 mg uridine/day when subjected to metabolic processes.

41. (Amended) The method of claim 39 wherein [the human suffers from] increasing said brain cytidine levels inhibits or ameliorates a neurological disorder.

42. (Amended) The method of claim 39 wherein [the human suffers from] increasing said brain cytidine levels inhibits or ameliorates a memory disorder.

44. (Amended) The method of claim 39 wherein [an] the effective amount of uridine or its precursor is administered at least once a day.

46. (Amended) The method of claim 39 which further comprises administering a therapeutically effective dose of [a second] at least one additional compound.

47. (Amended) The method according to claim 46 wherein said [second] at least one additional compound is choline, a choline salt, CDP-choline, lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, glycerophosphatidylcholine, or mixtures thereof.

49. (Amended) The method of claim 46 wherein said [second] at least one additional compound is a uridine phosphorylase inhibitor, uridine secretion inhibiting compound, uridine renal transport competitor, or combinations thereof.